AR201-13895

Jodi Burgess
08/01/2002 01:11 PM

To:
cc:
Subject:

tadams@chemintox.com on 08/01/2002 11:03:01 AM

To: Rtk Chem/DC/USEPA/US@EPA
cc:
Subject: Test Plan and Robust Summaries for Phenethyl Alcohol

Dear: Ms. Whitman:

On behalf of the Flavor and Fragrance High Production Volume Consortia (FFHPVC), I wish to submit the submission letter, test plan and robust summaries for the chemical designated "Phenethyl Alcohol".

The test plan and robust summaries are submitted in pdf. files. We will provide you with a hard copy of these documents upon request.

If there is a problem with the electronic transfer of these files, please feel free to contact me at any time.

Respectfully,
Timothy B. Adams Ph.D.
Technical Contact Person for FFHPVC

Thank you,
Tim Adams

- Submission Letter for Phenethyl alcohol.pdf
- Test Plan Phenethyl alcohol rev.pdf
- Robust Summaries for Phenethyl alcohol.pdf

The Flavor and Fragrance High Production Volume Consortia (FFHPVC)

1620 I Street, N.W.
Suite 925
Washington D.C. 20006
Tel. (202)-293-5800 Fax (202)-463-8998

August 1, 2002

Christie Todd Whitman, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

Dear Ms. Whitman:

On behalf or the member companies of the Aromatic Consortium, the Flavor and Fragrance High Production Volume Consortia is pleased to submit the Test Plan and Robust Summaries for the chemical designated "Phenethyl alcohol" to the HPV Challenge Program, AR-201. The Aromatic Consortium has chosen not to belong to the HPV Tracker System for submission of test plans and robust summaries. We are therefore submitting the test plan and accompanying robust summaries directly to EPA to make available to the public.

This submission includes one electronic copy in .pdf format. Hard copy can be provided upon request. The EPA registration number for the Aromatic Consortium is .

Please feel free to contact me with any questions or comments you might have concerning the submission at tadams@therobertsgroup.net, tadams@chemintox.com or 202-331-2325.

Sincerely,

Timothy Adams, Ph.D.
Technical Contact Person for FFHPVC

AR201-13895A

The Flavor And Fragrance High Production Volume Consortia

The Aromatic Consortium

Test Plan For Phenethyl alcohol

Phenethyl alcohol **CAS No. 60-12-8**

FFHPVC Aromatic Consortium Registration Number

Submitted to the EPA under the HPV Challenge Program by:
The Flavor and Fragrance High Production Volume Chemical Consortia
1620 I Street, NW, Suite 925
Washington, DC 20006
Phone: 202-331-2325
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List of Member Companies

BASF

EASTMAN CHEMICAL COMPANY

FIRMENICH, INCORPORATED

GIVAUDAN CORPORATION

HAARMANN & REIMER CORPORATION

INTERNATIONAL FLAVOR & FRAGRANCES, INC.

KOSA

LYONDELL CHEMICAL COMPANY

POLAROME INTERNATIONAL

PROCTOR & GAMBLE

QUEST

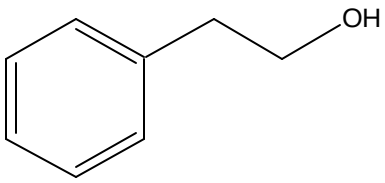
RHODIA INC.

SUMITOMO CHEMICAL COMPANY

Table of Contents

The HPV Challenge Test Plan for Phenethyl alcohol

1 IDENTITY OF SUBSTANCE



Phenethyl alcohol

$C_8H_{10}O$

CAS No. 60-12-8

Synonyms:

Benzeneethanol
Ethanol, 2-phenyl-
(2-Hydroxyethyl)benzene
PEA
beta-Phenethyl alcohol
2-Phenylethanol

2 CHEMICAL ANALYSIS

2.1 Introduction

In October of 1999, members of the United States flavor and fragrance industries as well as other manufacturers that produce source materials used in flavors and fragrances formed consortia of companies in order to participate in the Chemical Right-to-Know Program. Members of these consortia are committed to assuring the human and environmental safety of substances used in flavor and fragrance products. The consortia are organized as the Flavor and Fragrance High Production Volume Consortia (FFHPVC). The Aromatic Consortium, as a member of the FFHPVC serves as an industry consortium to coordinate testing activities for aromatic substances under the Chemical Right-to-Know Program. Fourteen (14) companies are current members of the Aromatic Consortium. The Aromatic Consortium and its member companies are committed to assembling and reviewing available test data, developing and providing test plans for each of the sponsored chemicals, and, where needed, conducting additional testing. The test plan, chemical analysis and robust summaries presented below are the first phase of the Aromatic Consortium's commitment to the Chemical Right-to-Know Program.

2.2 Background Information

Phenethyl alcohol (PEA) or 2-phenylethanol is a simple aromatic primary alcohol. It is currently permitted by the U.S. Food and Drug Administration (FDA) for direct addition to food for human consumption as a flavoring substance and is considered by the Flavor and Extract Manufacturers' Association (FEMA) Expert Panel to be "generally recognized as safe" (GRAS) for its intended use as a flavoring substance [Hall, 1960]. In addition, a group of 42 phenethyl alcohol, phenylacetaldehyde, phenylacetic acid and related phenethyl esters and acetals have been approved for use as flavoring agents by both the FDA (CFR 172.515) and the World Health Organization's Joint Expert Committee on Food Additives [JECFA, 2002].

Phenethyl alcohol occurs naturally in more than 200 foods [Maarse *et al*., 2000]. Quantitative natural occurrence data indicate that oral intake of phenethyl alcohol occurs predominantly from consumption of foods such as beer, wine, whiskey, olive oil, grapes, green and black tea, apple juice and coffee [Stofberg and Grundschober, 1987]. It has been estimated that approximately 700,000 kg of phenethyl alcohol is consumed annually as a natural component of foods.

Phenethyl alcohol is the main component of rose oil and is also found in neroli oil, ylang-ylang oil, carnation oil, and geranium oils. Therefore, phenethyl alcohol is used as a fragrance ingredient because of its rose-like odor in a wide variety of consumer products ranging from hydroalcoholic (typically in 70% ethanol) type products such as colognes and *eaux de toilette*, to cosmetics, soaps and detergents [Opdyke, 1975]. Such uses consumed approximately 1,000,000 pounds (lbs)/year in 1975 [Opdyke, 1975].

Phenethyl alcohol is also used as a flavor ingredient with an annual volume of use reported to be 2500 kg/year in the USA and 9900 kg/year in Europe [Lucas *et al*., 1999; IOFI, 1995]. Therefore, greater than 99% of oral intake of phenethyl alcohol occurs from consumption of food containing naturally occurring phenethyl alcohol compared to the intake from its intentional use as a flavoring substance.

Phenethyl alcohol may be synthesized by a variety of methods including a Friedel-Crafts reaction of benzene and ethylene oxide, and by hydrogenation of styrene oxide [Bauer and Garbe, 1985].

2.3 Reactivity and Metabolism

When ingested in traditional foods or intentionally added as a flavor ingredient of food, phenethyl alcohol is rapidly absorbed from the gastrointestinal tract. Once absorbed, phenethyl alcohol is oxidized to yield phenylacetic acid that is subsequently conjugated and excreted in the urine [Williams, 1959; El Marsy *et al*., 1956; James *et al*., 1972; Caldwell, 1987; Sangster and Lindley, 1986; Hawkins and Mayo, 1986].

Phenethyl alcohol is readily oxidized to phenylacetaldehyde by an assortment of NAD^+-dependent alcohol and aldehyde dehydrogenases [Bosron and Li, 1980]. The highest

activity of mammalian alcohol dehydrogenases (ALDH) occurs in the liver where they exhibit broad substrate specificity for the oxidation of primary aliphatic and aromatic alcohols. Human liver ALDH shows decreased K_m[1] with increasing lipophilicity. However, V_{max}[2] remains essentially constant suggesting that the rate-limiting step does not involve the binding or release of the alcohol or aldehyde intermediate [Pietruszko *et al*., 1973].

Once formed, phenylacetaldehyde is oxidized by inducible aldehyde dehydrogenases from rat liver cytosol. In the rat, these isoenzymes can be induced by phenobarbital [Simpson *et al*., 1985]. The K_m and V_{max} values of human mitochondrial aldehyde dehydrogenase (ALDH-2) and cytosolic isoenzyme (ALDH-1) for oxidation of phenylacetaldehyde indicate rapid conversion to phenylacetic acid [Klyosov, 1996].

Phenylacetaldehyde, 3- and 4-chlorophenylacetaldehyde are effectively oxidized to the corresponding phenylacetic acid derivatives when incubated with rat hepatic microsomal dehydrogenase containing NAD^+ as a coenzyme. The rates of oxidation for the 3- and 4-chloro derivatives are markedly slower than that of the parent phenylacetaldehyde [Martini and Murray, 1996]. In dogs, 32% of a 1,900 mg/kg bw dose of phenylacetaldehyde (No. 1002) given to dogs is rapidly oxidized and excreted as the glycine conjugate within 48 hours [Kay and Raper, 1922].

Phenylacetic acid is a normal component of human urine (250-500 mg/24 hours) and human blood (500 ng/ml) [Sandler *et al*., 1982], forming mainly from the breakdown of phenylalanine by intestinal bacteria [Seakins, 1971] or *via* oxidative deamination of endogenous phenethylamine [Seakins, 1971; Richter, 1938]. The following studies demonstrate that the metabolism and excretion of phenethyl alcohol occur *via* a pathway used by humans and other animals to metabolize endogenous substances. When administered orally, phenethylamine is rapidly metabolized to phenylacetylglutamine. Two human subjects, each fed a 300 mg dose of S-phenethylamine, excreted 60-62% of the administered dose as conjugated phenylacetic acid in the urine within 2 - 4.5 hours

[1] The Michaelis-Menten constant, K_m, is the concentration of the specific substrate at which a given enzyme yields one-half its maximum velocity. Michaelis-Menten equation: $v_0 = V_{max}[S]/K_m+[S]$ where v_0=initial rate at substrate concentration [S].

[Seakins, 1971; Richter, 1938]. Also, greater than 80% of [^{14}C]-S-phenethylamine fed to mice was rapidly excreted from urine as the glutamine conjugate of [^{14}C]-phenylacetic acid [Block, 1953].

In humans, 26% of a 4,000 mg oral dose of phenethyl alcohol (No. 987) is excreted in urine as the glutamine conjugate of phenylacetic acid within 24 hours [Thierfelder and Schempp, 1917]. In rabbits, 42% and 5% of a single 300 mg/kg bw oral dose of phenethyl alcohol is excreted in the urine as glycine and glucuronic acid conjugates, respectively, of phenylacetic acid within 24 hours. The ether soluble acid extracted from the 24-hour urine accounted for 61% of the dose [Bray *et al.*, 1958]. In an earlier study, 77% of 1300 mg/kg bw dose of phenethyl alcohol administered to rabbits *via* gavage was isolated from the 24-hour urine as an ether soluble acid. No appreciable quantity (less than 0.5%) of free phenylacetic acid was recovered [Bray *et al.*, 1946]. In another study it was reported that only 0.4 – 3.1% of an oral dose of phenylacetic acid was excreted unconjugated in the urine of rabbits [Tulane and Lewis, 1933].

Greater than 98% of a single oral dose of 80 mg of [carboxy-^{14}C]-phenylacetic acid administered to each of three healthy human volunteers and three patients exhibiting phenylketonuria was excreted in the urine within 24 hours as the glutamine conjugate [James *et al.*, 1973]. Greater than 98% of a 1 mg/kg oral dose of [carboxy-^{14}C]-phenylacetic acid given to two male volunteers was excreted in the urine within 24 hours [James *et al.*, 1972]. Based upon the results of studies using radiolabelled phenylacetic acid, it may be concluded that phenylacetic acid is rapidly absorbed and excreted within 24 hours.

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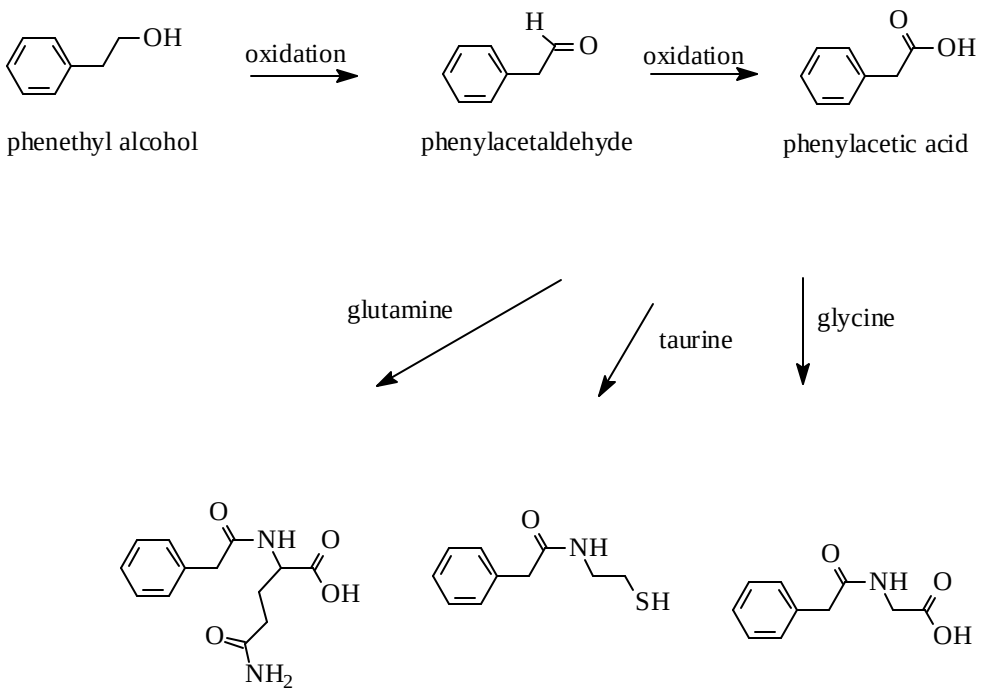
[2] V_{max} is the maximum rate or velocity of an enzymatic reaction which is indicative of all of the enzyme active site(s) is complexed with substrate.

FIGURE 1. METABOLISM OF PHENETHYL ALCOHOL



3 TEST PLAN

3.1 Chemical and Physical Properties

3.1.1 Melting Point

The measured melting point of phenethyl alcohol has been reported to be –27 °C [CRC, 1986; Merck, 1996]. Based on the input data of –27 °C, the calculated melting point of phenethyl alcohol is reported to be –6.0 ^{o}C (adapted Joback method) [MPBPVP EPI Suite, 2000a].

3.1.2 Boiling Point

The measured boiling point of phenethyl alcohol has been reported to be 218 ^{o}C [CRC, 1986] and 219 - 221 ^{o}C at 750 mm Hg [Merck, 1996]. Based on input values of 218.2 ^{o}C for boiling point and -27 ^{o}C for melting point, the calculated boiling point is 224.8 ^{o}C (adapted Stein and Brown Method) [MPBPVP EPI Suite, 2000a].

3.1.3 Vapor Pressure

Two measured values for vapor pressure of phenethyl alcohol are in good agreement. The vapor pressure has been reported to be 0.0868 mm Hg at 25 °C [MPBPVP EPI Suite, 2000b] and 0.0707 mm Hg at 30 °C [Vuilleumier, 1995]. Based on input values of 218.2 ^{o}C for boiling point and -27 ^{o}C for melting point, the calculated vapor pressure is 0.0222 mm Hg at 25 °C [MPBPVP EPI Suite, 2000a].

3.1.4 n-Octanol/Water Partition Coefficients

The reported log Kow of phenethyl alcohol is 1.36 [Sangster, 1989; KOWWIN EPI Suite, 2000b]. Log Kow was also calculated resulting in a value of 1.57 [KOWWIN EPI Suite, 2000a]. The agreement between measured and calculated values confirms the experimental value of log Kow for phenethyl alcohol of 1.36.

3.1.5 Water Solubility

The measured water solubility for phenethyl alcohol is 22,200 mg/L [WSKOWWIN EPI Suite, 2000b] and 20,340 mg/L [Merck, 1996]. Based on an experimental melting point of –27 ^{o}C and a log Kow of 1.36, the calculated water solubility is reported to be 3,272 mg/L at 25 ^{o}C [WSKOWIN EPI Suite, 2000a].

3.1.6 New Testing Required

None.

3.2 Environmental Fate and Pathways

3.2.1 Photodegradation

The calculated photodegradation half-life for phenethyl alcohol is 12.6 hours [AOPWIN EPI Suite, 2000]. The calculations are based on measured rate constants for radical reactions of OH, O_3 and NO_3 with organic substrates [AOPWIN EPI Suite, 2000]. The short half-life is consistent with the presence of reactive benzylic hydrogen and alcoholic OH function in phenethyl alcohol. Therefore, the half-life can be considered reliable.

3.2.2 Stability in Water

Phenethyl alcohol will not hydrolyze in water. The molecule is expected to be stable in water.

3.2.3 Biodegradation

Phenethyl alcohol has been subjected to a CO_2 production test according to OECD Guideline 301B [Quest International Ltd., 1994]. The total biodegradation was 106.3% after 28 days with 10% degradation in approximately 1 day. Phenethyl alcohol can be considered to be readily and ultimately biodegradable.

The calculated value of 103.0% linear biodegradation probability is in agreement with experimental values [BIOWIN EPI Suite, 2000].

3.2.4 Fugacity

Transport and distribution in the environment were modeled using Level III Fugacity-based Environmental Equilibrium Partitioning Model [Mackay, 1996a; 1996b] through the EPA EPI Suite 2000 program. The input parameters used were molecular weight, measured melting point (-27 °C), boiling point (218.2 °C), vapor pressure (0.089 mm Hg at 25 °C), water solubility (20,340 mg/L) and log Kow (1.36).

The model predicts that phenethyl alcohol is distributed mainly to the soil (52%) and water (42%) [Mackay, 1996a; 1996b].

In these environmental compartments, released phenethyl alcohol exhibits a potential to be oxidized to the corresponding carboxylic acid. Because of its use in food and cosmetics, soaps and detergents, the majority of phenethyl alcohol will enter the environment primarily *via* a sewage treatment plant and will be rapidly and extensively biodegraded.

3.2.5 New Testing Required

None. Phenethyl alcohol has been shown to be readily and ultimately biodegradable. While fugacity calculations estimate that the bulk will end up in soil and water, this does not take into account the principal uses of phenethyl alcohol, which would result in exposure *via* a sewage treatment plant allowing for rapid and extensive biodegradation.

3.3 Ecotoxicity

3.3.1 Acute Toxicity to Fish

Phenethyl alcohol has been subjected to a 96-hour static acute toxicity test according to the German guideline 38-414 with Golden Orfe *(Leuciscus idus*). An LC50 of between 220 mg (0 mortality) and 460 mg (100% mortality) was reported [BASF AG, 1988c]. The experimental value [ECOSAR EPI Suite, 2000] of LC50 of 230 mg/L is conservative since it approximates experimental LC0 value.

3.3.2 Acute Toxicity to Invertebrates

Phenethyl alcohol has been subjected to a 48-hour acute toxicity guideline study with *Daphnia magna*. A 48-hour EC50 of 287 mg/L was reported [BASF AG, 1988a]. The calculated [ECOSAR EPI Suite, 2000] LC50 of 239 mg/L is in the same range as the measured value.

3.3.3 Acute Toxicity to Aquatic Plants

Phenethyl alcohol has been subjected to a 72-hour growth inhibition test with algae (*Scenedesmus subspicatus*). The reported EC50 was 490 mg/L [BASF AG, 1988b]. The model value for the 96-hour EC50 is 146 mg/L [ECOSAR EPI Suite, 2000]. Although the model prediction is more conservative, it is on the same order of magnitude as the measured value.

3.3.4 New Testing Required

None. The acute aquatic toxicity of phenethyl alcohol has been well characterized in fish, invertebrates and plants and indicates a low order of toxicity.

3.4 Human Health Data

3.4.1 Acute Toxicity

Phenethyl alcohol has been subjected to acute oral, dermal, inhalation and intraperitoneal tests in rats, mice, rabbits, and guinea pigs. The rat oral LD50 values range from 1500 mg/kg bw to 2540 mg/kg bw [Jenner *et al*., 1964; Carpenter *et al*., 1974; Zaitsev and Rakhmanina, 1974; International Flavors & Fragrances, Inc., 1982; Moreno, 1982a].

The reported dermal LD50 values are in considerable disagreement ranging from 805 mg/kg [Carpenter *et al*., 1974] to 2535 mg/kg in the rabbit [International Flavors & Fragrances, Inc., 1983] to greater than 5000 mg/kg in the rat [Moreno, 1982b]. The intermediate value, 2535 mg/kg is from the best-documented study and is most consistent with what would be expected based on the dermal penetration in rabbits of 46-56% obtained from a pharmacokinetic study (Hawkins *et al*., 1987, no robust summary provided) and the oral LD50 values discussed above.

An acute inhalation exposure of phenethyl alcohol aerosol in rats for a 4-hour period followed by a 14-day observation resulted in no deaths and the LC50 was reported to be greater than 4.63 mg/L [Breckenridge *et al*., 1980].

Based on these data, it is concluded that phenethyl alcohol exhibits a very low acute toxicity.

3.4.2 Genetic Toxicity

3.4.2.1 In vitro Genotoxicity

No evidence of mutagenicity was observed when phenethyl alcohol [Florin *et al*., 1980] was incubated with *Salmonella typhimurium* (SAL) strains TA98, TA100, TA1535 and TA1537 with and without S-9 metabolic activation at concentrations up to and including 3 micromol/plate. No increase in a sister chromatid exchange was observed when human whole-blood lymphocyte cultures were exposed to 2-phenethyl alcohol for 72 hours

[Norppa and Vainio, 1983]. Also, no increase in unscheduled DNA synthesis was noted when rat hepatocytes were incubated with its principal metabolite phenylacetic acid [Heck *et al*., 1989].

3.4.2.2 In vivo Genotoxicity

In vivo mutagenicity and genotoxicity data exist for two structurally related substances that participate in the same metabolic pathway as phenethyl alcohol. One is a phenylacetic acid ester, isoeugenol phenylacetate and the other is 2-methyl substituted phenylacetaldehyde. Phenylacetic acid esters undergo hydrolysis prior to absorption. The methyl, ethyl, isopropyl, isoamyl, citronellyl esters of phenylacetic acid are rapidly hydrolyzed *in vitro* in simulated gastric juice and pancreatic juice [Longland *et al*., 1977] or in a buffered solution of pancreatin [Grundschober, 1977]. Once formed phenylacetic acid is excreted as the glutamine conjugate.

Given the rapid rate of formation of phenylacetaldehyde derivatives from the corresponding phenethyl alcohol derivatives *in vivo* [Bosron and Li, 1980; Pietruszko *et al*., 1973] and the rapid conversion of phenylacetaldehyde derivatives to phenylacetic acid metabolites [Martini and Murray, 1996], the structurally related aldehyde participates in the same metabolic pathway utilized by phenethyl alcohol.

None of the two structurally related substances (a phenethyl aldehyde and phenylacetic acid ester) showed any evidence of genotoxicity in well-recognized *in vivo* assays (mouse micronucleus and sex-linked recessive lethal assay). In mammals, substances were administered orally, by gavage, or by intraperitoneal injection at doses that were significant fractions of the reported lethal dose levels.

No increase in the frequency of sex-linked recessive mutations occurred in a three brood study when *Drosophila melanogaster* were maintained on 10 mM of phenylacetaldehyde, 2-methyl or 25 mM solutions of phenylacetic acid, isoeugenol ester for 3 days [Wild *et al.*, 1983].

In two clastogenicity assays, groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 564, 987, or 1,410 mg/kg bw of

phenylacetic acid, isoeugenol ester or at 0 hours with 134, 401, or 670 mg/kg bw of phenylacetaldehyde, 2-methyl [Wild *et al.*, 1983]. At 30 hours, the mice were sacrificed and bone marrow smears were prepared using the staining method of Schmid (1976). There was no evidence of micronucleated polychromatic erythrocytes for treated or control groups.

Based on the results of this *in vivo* genotoxicity assays for a structurally related phenethyl aldehyde and phenylacetate ester and the lack of any evidence of genotoxicity for numerous *in vitro* assays with and without metabolic activation for phenethyl alcohol, it is unlikely that phenethyl alcohol would exhibit a significant genotoxic potential *in vivo*. No additional *in vitro* and *in vivo* assays are requested for this substance.

Given that the *in vitro* and *in vivo* results consistently demonstrate that the substances exhibit a low order of genotoxic potential, no additional studies are required.

3.4.3 Repeated Dose Toxicity

A 90 day dermal toxicity study has been reported for phenethyl alcohol at daily doses of 250, 500, 1,000 or 2,000 mg/kg bw. The two highest dose groups exhibited a statistically significant lower growth rate than controls but with no significant differences in degree: final body weights (g) 1 g/kg males 482 ± 56, females 276 ± 16; 2 g/kg males 484 ± 43, females 272 ± 16. There was also a statistically significant decrease in hemoglobin and white blood cell count in males at the high dose. No significant effects on clinical examination, hematology, urinalysis or histopathological examination were seen. The no observable adverse effect level (NOAEL) was concluded to be 500 mg/kg bw/day [Owston, *et al*., 1981]. Based on the high dermal penetration of phenethyl alcohol on rats (70% after 5 daily repeated doses of 140 mg/kg bw; Hawkins *et al*., 1986, 1988, 1990), this translated to an internal dose of 350 mg/kg bw/day.

There are no acceptable oral repeated dose studies with phenethyl alcohol, however, the lack of serious effects in the dermal 90-day study combined with the high degree of dermal penetration make this an acceptable alternative. Furthermore, a 17-week study is available for a phenethyl ester that hydrolyzes to phenethyl alcohol and phenylacetic acid prior to absorption [Longland *et al*., 1977; Grundschober, 1977]. For 17 weeks, rats were

maintained on diets containing 1,000, 2,500 or 10,000 ppm of phenethyl phenylacetate. These dietary levels were calculated to provide an average daily intake of approximately 50, 125 or 500 mg/kg bw/day. No adverse effects were observed at any of the three dietary levels [Hagan *et al*., 1967]. While this study was conducted prior to GLP, it was conducted by the U.S. Food and Drug Administration and can be classified as highly reliable.

Additionally, a study of phenethyl alcohol in a mixture is available. Groups of male and female Wistar albino rats (20/sex/group) were given a mixture of compounds dissolved in tap water as their only drinking source for 56 weeks. This mixture included 6,000 mg/kg bw ethyl alcohol (6%), 4 mg/kg bw ethyl acetate (0.004%), 120 mg/kg bw isoamyl alcohol (0.12%), 120 mg/kg bw phenethyl alcohol (0.12%), 200 mg/kg bw isobutyl alcohol (0.2%), and 200 mg/kg bw acetic acid (0.2%)[3]. A control group of 20 rats/sex was maintained on tap water only. Body weights were recorded weekly. The activity of alcohol dehydrogenase (ADH), glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and the protein content were determined at two-four week intervals in the livers of rats. At study termination, liver, kidney, heart, spleen, and lung were examined histologically. There was no difference in absolute or relative liver weight between the test and control groups. There was a slight increase in GOT activity between 28 and 56 weeks in both the test and control groups. Histopathological examination revealed no significant abnormalities in any of the organs examined. The authors concluded that the mixture of chemicals containing phenethyl alcohol did not produce any effects in the parameters tested [Johannsen and Purchase, 1969].

3.4.4 Reproductive Toxicity

A reproductive/developmental screening test has been performed for the principal metabolite phenylacetic acid. The lack of toxicity to reproductive organs in subchronic toxicity tests (see section 3.4.3), the lack of developmental toxicity in females in numerous developmental studies at high dose levels of phenethyl alcohol, indicate that phenethyl alcohol exhibits a low order of reproductive toxicity.

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[3]Conversions of dose based on FDA, 1993.

Four groups of 10 virgin Crl CD rats were administered oral dose levels of 0, 250, 500, or 1,000 mg/kg bw of phenylacetic acid by gavage once daily, 7 days prior to cohabitation, through cohabitation (maximum of 7 days), gestation, delivery, and a 4-day post-parturition period. The duration of the study was 39 days [Vollmuth *et al.*, 1995]. Maternal indices monitored included twice-daily clinical observation, measurement of body weights, food consumption, duration of gestation, and fertility parameters (mating and fertility index, gestation index, number of offspring per litter). Offspring indices included daily observation, clinical signs, examination for gross external malformations, and measurement of body weight.

At 250, 500 and 1,000 mg/kg in dams, a significant (P less than 0.05) decrease in body weight and absolute and relative food consumption was reported during the premating period. Clinical signs of toxicity and a statistically significant increase in mortality was recorded in the mid- and high dose groups, but not in the low dose dams. Necropsy of dams showed gross lesions in the mid- and high-dose groups. Measurements of mating success and fertility were similar for controls, low-dose and mid-dose groups. No changes in fertility index, averages for duration of cohabitation or gestation, gestation index, implantation sites, litter size, or pup sex ratios were seen at any dose levels. The only reproductive parameter affected was a decrease in the number of females mated per number of females pregnant at the 1000 mg/kg bw level. Based on the toxicity and increased dam mortality at the two highest dose levels and a decrease in mating index in the mid-dose group, the maternal reproductive effects were reported at 500 and 1,000 mg/kg bw/day. The dose level of 250 mg/kg bw/day had no adverse effects on the reproductive performance of female Sprague-Dawley rats [Vollmuth *et al.*, 1995].

3.4.5 Developmental/Teratogenicity Toxicity

Screening studies performed by one group of investigators during the 1980's reported that low dose levels of phenethyl alcohol and phenylacetic acid produce teratogenic effects resembling Fetal Alcohol Syndrome [Mankes *et al*., 1983]. (Mankes, 1984 and 1985 were presentation abstracts and no robust summaries provided). These results are contradicted by the results of another study in which phenethyl alcohol given to pregnant rats at high doses at critical periods of embryogenesis do not cause any visible anomalies

in embryonal development [Bottomley *et al.*, 1987]. More recent comprehensive studies conducted with high dose levels of phenethyl alcohol given either by oral [Bottomley *et al.*, 1987] and dermal [Palmer *et al.*, 1986] routes of exposure have demonstrated that this group of substances exhibits a very low order of developmental toxicity.

In the original studies [Mankes *et al.*, 1983, 1984 and 1985], pregnant Long Evans rats were given oral doses of 4.3, 43 or 432 mg/kg of phenethyl alcohol by gavage during days 6 to 15 of gestation. The average birth weight and pup size of all treated groups were significantly lower than those of the control group, but the change was not dose-related. In fact, birth weights were greater in the mid-dose group than in controls. Mean litter size was greater in the high dose group (13) than in either the two lower doses (9) or controls (12). Also, embryolethality did not occur in the high dose group but was 18% at 43 mg/kg and 10% at 4.3 mg/kg. The authors reported a clear dose related increase in the percentage of malformations in live offspring (100% at the 432 mg/kg level, 93% at 43 mg/kg and 50% at 4.3 mg/kg). Malformations were mainly in ocular malformation, neural tube defects, hydronephrosis and limb defects [Mankes *et al.*, 1983]. In abstracts of subsequent studies reported by the same authors [Mankes *et al.*, 1984; 1985], dose levels of phenethyl alcohol equivalent to 0.02% and 24% of the oral LD50 were administered to pregnant Long Evans rats. Intrauterine growth retardation (birth weight reductions) and embryolethality were reported at all dose levels. These observations are inconsistent with those of the original study.

The effects of dietary administration of microencapsulated phenethyl alcohol on pregnancy of the rat was studied [Bottomley *et al.*, 1987] according to a protocol essentially the same as OECD 414. The test diet containing nominal 0 (control), 1,000, 3,000, or 10,000 ppm (approximately 0, 50, 150, or 500 mg/kg bw) was made available to the rats during days 6 to 15 of pregnancy. Spray-dried gum Arabic, the microencapsulant, was used as a placebo control and was also added to the lower concentrations so that the total inclusion level remained constant for all groups at 5%. The animals were killed on day 20 post coitum and *in utero* development assessed by determination of litter values and examination of the fetuses for structural malformations or anomalies. Achieved intake of phenethyl alcohol was calculated for dams during the treatment period, values were adjusted to take account of the assayed content of test

material in the microcapsules used and indicated that the actual intake was about 83, 266, and 799 mg/kg per day for groups designated 1,000, 3,000 and 10,000 ppm, respectively. The treatment of the dam with phenethyl alcohol by dietary inclusion of 799 mg/kg had a negligible detrimental effect on *in utero* development. Although there was clear evidence of impaired weight gain in dams following initial exposure to the test material, fetal development was virtually unaffected, the only possible exception being a marginal delay in the ossification process, an event that the authors indicated is usually transient and self-correcting during postnatal maturation. At 83 and 266 mg/kg, phenethyl alcohol did not elicit any overt response in the dam and embryofetal development and morphology was unaffected [Bottomley *et al.*, 1987].

The effect of phenethyl alcohol on pregnancy of rats was studied following a similar protocol to OECD 414. Phenethyl alcohol was applied topically at the dose of 0, 0.14, 0.43 or 1.40 ml/kg during day 6 to 15 of pregnancy. The doses are approximately equal to 0, 140, 430, and 1400 mg/kg bw, respectively, and were chosen so that the intermediate dose was roughly equivalent to the highest dosage used in a previous oral study [Mankes *et al*., 1983]. The highest dose was designed to extend the range in case of differential absorption by the dermal route. The animals were killed on day 20 of pregnancy and *in utero* development assessed by determination of litter values and examination of the fetuses for soft tissue and skeletal changes. At 1.40 ml/kg per day, there was clear evidence of both maternal toxicity including lethality, suppression of mean food intake and growth rate and embryo-fetal toxicity indicated by resorption, embryo-fetal wastage, reduction in mean litter size, depression of fetal weight, a wide range of soft tissue and skeletal changes, incomplete ossification. For the latter, the pattern of response and the comprehensive nature of the morphological changes were considered by the authors, to be beyond those that would occur merely as a secondary consequence of the maternal response. In this study, 0.43 ml/kg per day was considered close to the threshold of maternal toxicity but while there was no evidence of an adverse effect on litter values, there was a dose-dependent increase in some of the morphological changes recorded in fetuses. A dose of 0.14 ml/kg per day did not elicit any adverse effects in the litter values. Based on the overt effects on fetal development at the higher dosages, the slight differences in morphological changes between the 0.14 ml/kg dose and controls (cervical

rib(s) thoracic vertebral irregularities), the authors concluded that the 0.14 ml/kg dose level (140 mg/kg bw) is a threshold for developmental toxicity in the rat [Palmer *et al*., 1986].

In order to better clarify the fetal NOAEL in the previous study, a limited developmental study was conducted by a similar protocol, but looking particularly at the cervical rib bud and thoracic vertebrae effects, pregnant rats were treated dermally with 70, 140, 280, 430 or 700 mg/kg bw/day on days 6 to 16 of pregnancy. Cervical rib buds were statistically significantly higher than controls at 700 mg/kg only and there were no significant incidences of vertebrae effects. However, significant and dose-related skin irritation was seen in the dams at all dose groups and delayed ossification (judged to be reversible) was seen in fetuses of all groups. The only statistically significant difference from controls in the two lower dose groups was incomplete ossification of the pelvis but with no dose correlation. These effects may have been secondary to the dermal irritation. No clear no observable effect level (NOEL) for dams or fetuses can be concluded from this study, however, the minor effects seen in the two lower doses could lead to a conclusion of a fetal NOAEL of 140 mg/kg bw [Christian *et al*., 1988].

In the reproduction/developmental screening test discussed in the section on reproductive toxicity, four groups of 10 virgin Crl CD rats were administered oral dose levels of 0, 250, 500, or 1,000 mg/kg bw of phenylacetic acid by gavage once daily, 7 days prior to cohabitation, through cohabitation (maximum of 7 days), gestation, delivery, and a 4-day post-parturition period. The duration of the study was 39 days [Vollmuth *et al.*, 1995]. Offspring indices monitored included daily observation, clinical signs, examination for gross external malformations, and measurement of mortality (number of stillborns), viability (pups dying on days 1-4), body weight and body weight gain. The only effects reported occurred at the 1000 mg/kg bw/day level. A statistically significant decrease in viability and a non-significant decrease in body weight gain were reported at the highest dose level. The dose level of 500 mg/kg bw/day had no adverse effects on the development of the offspring of female Sprague-Dawley rats.

3.4.6 New Testing Required

None.

3.5 Test Plan Table

Chemical	Physical-Chemical Properties				
	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
CAS No. 60-12-8 Phenethyl alcohol	**A, Calc**	**A, Calc**	**A, Calc**	**A, Calc**	**A, Calc**

Chemical	Environmental Fate and Pathways			
	Photodegra-dation	Stability in Water	Biodegra-dation	Fugacity
CAS No. 60-12-8 Phenethyl alcohol	**Calc**	**NA**	**A, Calc**	**Calc**

Chemical	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Invertebrates	Acute Toxicity to Aquatic Plants
CAS No. 60-12-8 Phenethyl alcohol	**A, Calc**	**A, Calc**	**A, Calc**

Chemical	Human Health Data					
	Acute Toxicity	Genetic Toxicity *In Vitro*	Genetic Toxicity *In Vivo*	Repeat Dose Toxicity	Repro-ductive Toxicity	Develop-mental Toxicity
CAS No. 60-12-8 Phenethyl alcohol	**A**	**A**	**R**	**A**	**R**	**A, R**

LEGEND

Symbol	Description
R	Endpoint requirement fulfilled using data for structurally related substances, SAR
T	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

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AR201-13895B

The Flavor And Fragrance High Production Volume Consortia

The Aromatic Consortium

Robust Summaries for Phenethyl alcohol

Phenethyl alcohol **CAS No. 60-12-8**

FFHPVC Aromatic Consortium Registration Number

Submitted to the EPA under the HPV Challenge Program by:

The Flavor and Fragrance High Production Volume Chemical Consortia

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List of Member Companies

BASF

EASTMAN CHEMICAL COMPANY

FIRMENICH, INCORPORATED

GIVAUDAN CORPORATION

HAARMANN & REIMER CORPORATION

INTERNATIONAL FLAVOR & FRAGRANCES, INC.

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QUEST

RHODIA INC.

SUMITOMO CHEMICAL COMPANY

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The Flavor and Fragrance High Production Volume Consortia

Robust Summaries for Phenethyl alcohol

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al*., 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 CHEMICAL AND PHYSICAL PROPERTIES

1.1 Melting Point

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Colorless liquid
Method/guideline	Measured
GLP	Ambiguous
Melting Point	-27 °C
Decomposition	No
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	CRC Handbook of Chemistry and Physics (1986) 67th edition, Robert C. Weast, editor, The Chemical Rubber Co Press, Inc. Boca Raton, FL.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Melting Point	-27 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc. Whitehouse Station, NJ.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/adapted Joback method
Melting Point	-6 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000a) US Environmental Protection Agency.

1.2 Boiling Point

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
GLP	Ambiguous
Boiling Point	218.2 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	CRC Handbook of Chemistry and Physics (1986) 67th edition, Robert C. Weast, editor, The Chemical Rubber Co Press, Inc. Boca Raton, FL.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Boiling Point	219 - 221 °C
Pressure	750 mm Hg
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc. Whitehouse Station, NJ.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/adapted Stein and Brown method
Boiling Point	224.8 °C
Pressure	750 mm Hg
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000a) US Environmental Protection Agency.

1.3 Vapor Pressure

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
GLP	Ambiguous
Year	1995
Remarks for Test Conditions	Study was conducted at 30 °C, skin temperature
Vapor Pressure	0.0707 mm Hg
Temperature	30 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Vuilleumier C., Flament I., and Sauvegrain P. (1995) Headspace analysis study of evaporation rate of perfume ingredients applied to skin. Inter. J. of Cos. Sci., 17, 61-76.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Vapor Pressure	0.0868 mm Hg
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	MPBPVP EPI Suite (2000b) US Environmental Protection Agency (Daubert T.E. and Danner, R.P., 1989).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/modified Grain method
Vapor Pressure	0.0222 mm Hg
Temperature	25 °C
Remarks for Test Conditions	Based on input parameters: boiling point - 218.2 °C.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000a) US Environmental Protection Agency.

1.4 n-Octanol/Water Partition Coefficients

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Experimental
GLP	Not applicable

Log Pow	1.36
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Sangster J. (1989) Octanol-water partition coefficients of simple organic compounds. J Phys. Chem. Ref. Data, 18(3), 1111-1229.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Log Pow	1.36
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	KOWWIN EPI Suite (2000b) US Environmental Protection Agency (Hansch C. *et al*., 1995).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/KOWWIN
Log Pow	1.57
Data Qualities Reliabilities	Reliability code 4. Not assignable
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000a) US Environmental Protection Agency.

1.5 Water Solubility

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/Guideline	Measured
Value (mg/L) at Temperature	22,200 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	WSKOWIN EPI Suite (2000b) US Environmental Protection Agency (Vivandi S.C. *et al*., 1981)

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/Guideline	Measured
Value (mg/L) at Temperature	20,340 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc. Whitehouse Station, NJ.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/Guideline	Calculated
Value (mg/L) at Temperature	3272 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWIN EPI Suite (2000a) US Environmental Protection Agency).

2 ENVIRONMENTAL FATE AND PATHWAYS

2.1 Photodegradation

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated
Test Type	AOPWIN
Halflife t1/2	12.6 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) U S Environmental Protection Agency.

2.2 Biodegradation

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	99.0% pure
Method	OECD Guideline 301B
Test Type	Sealed vessel carbon dioxide production test
GLP	Yes
Year	1994
Contact Time	28 days
Innoculum	Secondary effluent from an unacclimatized activated sludge plant at URL north.
Remarks for Test Conditions	Test material was directly added to the incubation mixture. The incubation was 28 days. The nominal concentration was 10 mg/l organic carbon. The test temperature range was 17-22 °C.
Degradation % After Time	106.3% after 28 days
Remarks Results	Biodegradation was 106.3% (103.3%-109.2%).

Time required for 10% degradation	1 day
10 day window criteria	Yes
Total degradation	Yes
Classification	Readily and ultimately biodegradable
Conclusion Remarks	Phenethyl alcohol was shown to be readily and ultimately biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Quest International Ltd. (1994) The ultimate biodegradability of phenylethyl alcohol in the sealed vessel test. Unpublished report.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated
Test Type	BIOWIN
Results	Probability of Rapid Biodegradation 1.03 (Linear Model) - 0.99 (Non-Linear). MITI Model 0.54 (Linear Model) - 0.71 (Non-Linear)
Conclusion Remarks	Expert Survey Biodegradation Results: Ultimate Survey Model: 3.0 (weeks) - Primary Survey 3.7 (days to weeks)
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

2.3 Fugacity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III

Input Parameters	MW, VP, log Kow, MP, water solubility, Henry's LC
Media	Air
Model Data and Results	Half-life = 25.3 hours
Estimated Distribution and Media Concentration	2.3%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Input Parameters	MW, VP, log Kow, MP, water solubility, Henry's LC
Media	Water
Model Data and Results	Half-life = 360 hours
Estimated Distribution and Media Concentration	46%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9),

1627-1637.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Input Parameters	MW, VP, log Kow, MP, water solubility, Henry's LC
Media	Soil
Model Data and Results	Half-life = 360 hours
Estimated Distribution and Media Concentration	51.6%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Input Parameters	MW, VP, log Kow, MP, water solubility, Henry's LC
Media	Sediment
Model Data and Results	Half-life = 1440 hours

Estimated Distribution and Media Concentration	0.09%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

3 ECOTOXICITY

3.1 Acute Toxicity to Fish

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 99.5%
Method/guideline	DIN 38 412 96 hour static toxicity
Test Type	Experimental
GLP	No
Year	1988
Species/Strain/Supplier	Golden Orfe (*Leuciscus idus*)
Exposure Period	96 hours
Analytical monitoring	None
Remarks for Test Conditions	Reconstituted fresh water according to guideline, 10 L at 21 °C. 10 fish/concentration. Appropriate statistical analyses were performed.
Reference substances	Chloroacetamide
Observations of Precipitation	No evidence of precipitation.
Endpoint value	LC50 = 220-460 mg/L
Nominal concentrations as mg/L	100, 215, 464, 1000 mg/L
Remarks fields for results	100% mortality at high dose after 1 hour and at 464 mg/L after 24 hour. No mortality at 2 lower concentrations.
Unit	mg/L
Conclusion Remarks	LC50 = 220-460 mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	BASF AG (1988c) Abteilung Toxikologie unpublished data. (87/410).

Substance Name	Phenethyl alcohol

CAS No.	60-12-8
Method/guideline	ECOSAR
Test Type	Calculated
GLP	Not Applicable
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Remarks for Test Conditions	Based on: melting point = -27 C; water solubility = 22,200 mg/L; KOW = 1.57.
Endpoint value	LC50 = 230 mg/L
Conclusion Remarks	LC50 = 230 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency, OPPT Risk Assessment Division (G. Cash & V. Nabholz, April 2001).

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 99%
Method/guideline	EPA EG1, 1982
Test Type	Experimental
GLP	No
Year	1988
Species/Strain/Supplier	*Daphnia magna Straus*
Analytical procedures	None
Test Details	48 hours
Nominal concentrations as mg/L	31.25, 62.5, 125,250, 500
EC50, EL50, LC0, at 24,48 hours	24 hour EC50 330 mg/L; 48 hour EC50 287 mg/L
Conclusion remarks	48 hour EC0 125 mg/L; EC100 500 mg/L

Biological observations	Inability to swim
Appropriate statistical evaluations?	Yes
Data Qualities Reliabilities	Code 1. Guideline study.
Data Reliability Remarks	Reliability code 1. Reliable without restriction.
Reference	BASF AG (1988a) Labor Oekologie. Unpublished report (0107/88).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	*Daphnia magna*
Test Details	48 hours
Remarks for Test Conditions	Based on: melting point = -27 C; water solubility = 22,200 mg/L; KOW = 1.57.
EC50, EL50, LC0, at 24,48 hours	LC50 = 239 mg/L
Conclusion remarks	LC50 = 239 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency, OPPT Risk Assessment Division (G. Cash & V. Nabholz, April 2001).

3.3 Acute Toxicity to Aquatic Plants

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Experimental
Test Type	72 hour growth inhibition test
GLP	No
Year	1988
Species/Strain/Supplier	*Scenedesmus subspicatus subspicatus*

Exposure Period	72 hour
Nominal concentrations as mg/L	200, 280, 400, 560, 800, 1600
NOEC, LOEC or NOEL, LOEL	NOEC 280
Biological observations	Biomass
Conclusion Remarks	EC10 - 300; EC50 - 490; EC90 - 790
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report that meets basic scientific principles.
Reference	BASF AG (1988b) Labor Oekologie, Unpublished data (1010/88).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated
Test Type	ECOSAR
GLP	Not Applicable
Species/Strain/Supplier	Green algae
Exposure Period	96 hour
Remarks for Test Conditions	Based on: melting point = -27 C; water solubility = 22,200 mg/L; KOW = 1.57.
Endpoint value	EC50 = 146 mg/L
Conclusion Remarks	EC50 = 146 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency, OPPT Risk Assessment Division (G. Cash & V. Nabholz, April 2001).

4 HUMAN HEALTH TOXICITY

4.1 Acute Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	Ambiguous
Year	1982
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
# of animals per sex per dose	5
Vehicle	0.25% methylcellulose
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Test material in 0.25% methylcellulose was given to groups of 10 (5/sex) Sprague-Dawley rats at 1000, 1600, 2000, 2500 & 3200 mg/kg following an 18 hour fast. Animals were observed immediately and at 1, 4 & 24 hours after dose & 2times/day for 14 days. LD50 with 95% confidence limits was determined by method of Litchfield and Wilcoxon (1949). Could not calculate the LD50 for females according to this method.
Value LD50 or LC50 with confidence limits	Male rat LD50 = 1692.9 mg/kg with 95% C.I. 1433.3-1998.9 mg/kg. Calculated LD50 for male and female rats = 1609 mg/kg 95% C.I. Of 1399.6-1850.4 mg/kg.
Number of deaths at each dose level	1000 mg/kg: No deaths; 1600mg/kg: 5/10 dead; 2000 mg/kg: 9/10 dead; 2500 mg/kg: 10/10 dead.
Conclusion Remarks	The oral LD50 in male and female rats was reported to be 1609 mg/kg 95% C.I. of 1399.6-1850.4 mg/kg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	International Flavors & Fragrances, Inc. (1982) Acute oral toxicity study of phenethyl alcohol in rats. Unpublished report.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8

Test Type	Acute oral LD50 study
GLP	No
Year	1974
Species/strain	Rat
Sex	Not reported
Route of Administration	Oral
Value LD50 or LC50 with confidence limits	Reported LD50 = 2.46 ml/kg or 2509 mg/kg
Conclusion Remarks	The oral LD50 for phenethyl alcohol in rats was reported to be 2.46 (1.79-3.39) ml/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles. Published in a peer-reviewed journal.
References	Carpenter C.P., Weil, C.S., and Smyth, H.F. (1974) Range-finding toxicity data: List VIII. Toxicology and Applied Pharmacology, 28, 313-319.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1963
Species/strain	Rats/Osborne-Mendel
Sex	Male and Female
Route of Administration	Oral-Gavage
Value LD50 or LC50 with confidence limits	LD50 = 1790 mg/kg. 95% C.I. 1580-2020 mg/kg; Slope = 1.2 (1.1-1.3).
Number of deaths at each dose level	Death from 4 to 18 hours.
Remarks for Test Conditions	Animals were subjected to an 18-hour predose fast. All doses were given by intubation. The animals were observed over a 2-week period for mortality and/or systemic effects. LD50 results were calculated per Litchfield-Wilcoxon (1949). No necropsy mentioned
Remarks for Results	Toxic signs were coma within 15 minutes. Gross pathology showed irritation of the lower half of the stomach on the higher doses.

Conclusion Remarks	The oral LD50 in rats was calculated to be 1790 mg/kg. 95% C.I. 1580-2020 mg/kg; Slope = 1.2 (1.1-1.3). Study was conducted prior to GLP or OECD guidelines but was reported by respected researchers at the FDA and published in a peer-reviewed journal.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles. Published in a peer-reviewed journal.
References	Jenner P.M., Hagan, E.C., Taylor, J.M., Cook, E.L. and Fitzhugh, O.G. (1964) Food flavorings and compounds of related structure I. Acute oral toxicity. Food and Cosmetics Toxicology, 2(3), 327-343.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	Ambiguous
Year	1982
Species/strain	Rat/Wistar
Sex	Male
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral
Remarks for Test Conditions	Animals were observed for 14 days.
Value LD50 or LC50 with confidence limits	Reported LD50 = 1500 mg/kg (C.I. 1200-2000 mg/kg)
Number of deaths at each dose level	Dose 760 mg/kg: 1/10 dead; 1200 mg/kg: 1/10 dead; 1900 mg/kg: 9/10 1.9 dead; 5000 mg/kg: 10/10 dead.
Conclusion remarks	The oral LD50 for phenethyl alcohol was calculated to be 1500 mg/kg (C.I. 1200 - 2000 mg/kg) in rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Moreno O. M. (1982a) Acute toxicity studies. Unpublished report to RIFM.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1974
Species/strain	Rat
Sex	Male and Female
# of Animals per Sex per Dose	6 males and 5 females
Vehicle	Sunflower oil
Route of Administration	Oral-Gavage
Remarks for Test Conditions	15-day observation period. Vehicle was sunflower oil.
Value LD50 or LC50 with confidence limits	Reported LD50 = 2540 mg/kg
Conclusion Remarks	The acute oral LD50 in rats was reported to be 2540 mg/kg.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Zaitsev A.N. and Rakhmanina, N.L. (1974) Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vop. Pitan, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1974
Species/strain	Mice
Sex	Male and Female
# of animals per sex per dose	6 males and 5 females
Vehicle	Sunflower oil
Route of Administration	Oral-Gavage
Remarks for Test Conditions	15-day observation period. Vehicle was sunflower oil.

Value LD50 or LC50 with confidence limits	Reported LD50 = 2540 mg/kg.
Conclusion Remarks	The acute oral LD50 in mice was reported to be 2540 mg/kg.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Data Reliabilities Remarks	Code 3. Documentation insufficient for assessment.
References	Zaitsev A.N. and Rakhmanina, N.L. (1974) Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vop. Pitan, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1963
Species/strain	Mice
Sex	Not reported
Route of Administration	Oral
Remarks for Test Conditions	Not reported
Value LD50 or LC50 with confidence limits	Reported LD50 = 800 -1500 mg/kg
Number of deaths at each dose level	Not reported
Conclusion Remarks	The acute oral LD50 in mice was reported to be 800 -1500 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1974

Species/strain	Guinea pig
Sex	Male and Female
# of animals per sex per dose	6 males and 5 females
Route of Administration	Oral-Gavage
Vehicle	Sunflower oil
Value LD50 or LC50 with confidence limits	Reported LD50 = 2540 mg/kg
Remarks for test conditions	15-day observation period. Vehicle was sunflower oil.
Conclusion Remarks	The acute oral LD50 in guinea pig was reported to be 2540 mg/kg.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Zaitsev A.N. and Rakhmanina, N.L. (1974) Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vop. Pitan, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1963
Species/strain	Guinea pig
Sex	Not reported
# of animals per sex per dose	Not reported
Route of Administration	Oral
Vehicle	Not reported
Value LD50 or LC50 with confidence limits	Calculated LD50 = 400 - 800 mg/kg
Conclusion Remarks	The acute oral LD50 value in guinea pig was calculated to be 400 - 800 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute dermal LD50 study
GLP	No
Year	1974
Species/strain	Rabbit
Sex	Not reported
Route of Administration	Dermal
Value LD50 or LC50 with confidence limits	Reported LD50 = 0.79 ml/kg or 805 mg/kg
Conclusion Remarks	The dermal LD50 for phenethyl alcohol in rabbits was reported to be 0.79 ml/kg (0.49-1.30) ml/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliabilities Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles. Published in a peer-reviewed journal.
References	Carpenter C.P., Weil, C.S., and Smyth, H.F. (1974) Range-finding toxicity data: List VIII. Toxicology and Applied Pharmacology, 28, 313-319.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute dermal LD50 study
GLP	Yes
Year	1982
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Dermal
Remarks for Test Conditions	5000 mg/kg was applied to the rat skin
Value LD50 or LC50 with confidence limits	LD50 greater than 5000 mg/kg
Number of deaths at each dose level	None

Conclusion Remarks	The dermal LD50 in rat was reported to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Moreno O. M. (1982b) Acute toxicity studied. Unpublished report to RIFM.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute dermal LD50 study
GLP	Ambiguous
Year	1983
Species/strain	Rabbits/New Zealand white
Sex	Male and Female
# of animals per sex per dose	4
Route of Administration	Dermal
Value LD50 or LC50 with confidence limits	LD50 = 2535 mg/kg (C.I. 1769-3634 mg/kg).
Remarks for Test Conditions	Test material at 1600, 2500 and 4000 mg/kg was applied to abraded and intact skin of groups of 8 (4/sex) New Zealand white rabbits. Test sites were washed after 24 hours. Observations recorded 2 & 4 hour later & twice daily thereafter for 14 days.
Number of deaths at each dose level	1600 mg/kg: 1/8 died; 2500 mg/kg: 5/8 died; 4000 mg/kg: 6/8 died.
Conclusion Remarks	The acute dermal LD50 value in rabbits was calculated to be 2535 mg/kg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	International Flavors & Fragrances, Inc. (1983) Acute dermal toxicity test of phenethyl alcohol in rabbits. Unpublished report.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute intraperitoneal LD50 study

GLP	No
Year	1963
Species/strain	Mice
Sex	Not reported
# of animals per sex per dose	Not reported
Route of Administration	Intraperitoneal
Value LD50 or LC50 with confidence limits	Reported LD50 = 200 - 400 mg/kg
Conclusion Remarks	The intraperitoneal LD50 value in mice was reported to be 200 - 400 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute intraperitoneal LD50 study
GLP	No
Year	1963
Species/strain	Guinea pig
Sex	Not reported
# of animals per sex per dose	Not reported
Route of Administration	Intraperitoneal
Value LD50 or LC50 with confidence limits	Calculated LD50 = 400 - 800 mg/kg
Conclusion Remarks	The intraperitoneal LD50 in guinea pig was calculated to be 400 - 800 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute inhalation LC50 study.
GLP	Ambiguous
Year	1980
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
# of animals per sex per dose	5
Vehicle	Aerosol
Route of Administration	Inhalation
Remarks for Test Conditions	After a 4-hour exposure the following observations were made over a 14-day period: mortality, clinical signs, body weight, gross and histopathology.
Value LD50 or LC50 with confidence limits	Acute inhalation LC50 was reported to be greater than 4.63 mg/L.
Number of deaths at each dose level	0/10 at 4.63 mg/L
Remarks for Results	The animals exhibited no clinical signs during or up to 14 days after exposure at 4.63 mg/L.
Conclusion Remarks	Acute inhalation LC50 for phenethyl alcohol in rats was reported to be greater than 4.63 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Breckenridge C., C.J.Collins, S.Qureshi and B.G.Procter (1980) The acute toxicity of inhaled phenyl ethyl alcohol in the albino rat. Unpublished report to RIFM.

4.2 Genetic Toxicity

4.2.1 *In vitro* genotoxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 97%

Method/guideline	Ames test
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	*Salmonella typhimurium* strains TA98, TA100, TA1535 & TA1537
Metabolic Activation	With and without S9 fraction rat liver treated with Aroclor 1254
Doses/Concentration	3 micromol/plate
Statistical Methods	Not given
Remarks for Test Conditions	The solvent used was ethanol. Only one replicate was performed for the substances, which tested negative. Similar to OECD 471. No *E. coli* strain was included.
Results	No effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate Statistical Evaluations	None given
Conclusion Remarks	No mutagenic activity of phenethyl alcohol was observed using *Salmonella typhimurium* strains TA98, TA100, TA1535 & TA153 in the presence or absence of S9 fraction.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions. Published in a peer-reviewed journal.
References	Florin I., Rutberg, L., Curvall, M. and Enzell, C. R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology, 18, 219-232.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 98%
Method/guideline	*In Vitro* Chromosome Aberration Test with Human Lymphocytes
Test Type	Sister Chromatid Exchange
System of Testing	Human lymphocytes
GLP	No

Year	1983
Species/Strain	Adult male human whole-blood lymphocytes
Metabolic Activation	None
Doses/Concentration	0.1, 0.5, 1, 5 & 10 mM
Statistical Methods	t-test
Remarks for Test Conditions	Vehicle was acetone
Results	No effects
Cytotoxic concentration	Approximately 5 mM
Genotoxic Effects	None
Appropriate statistical evaluations?	Yes
Conclusion Remarks	Phenethyl alcohol was unable to induce Sister-Chromatid Exchange in whole-blood lymphocyte cultures of a healthy male donor.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Norppa H. and Vainio, H. (1983) Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. Mutation Research, 116, 379-387.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	The test substance was phenylacetic acid, principal metabolite of phenethyl alcohol *in vivo*.
Method/guideline	Unscheduled DNA Synthesis Assay (UDS)
Test Type	Unscheduled DNA synthesis
System of Testing	Rat hepatocytes
GLP	Not given
Year	1989
Species/Strain	Rat/Fischer and Sprague-Dawley adult male
Metabolic Activation	No
Doses/Concentration	1500 micrograms
Statistical Methods	Not given

Remarks for Test Conditions	Livers were perfused *in situ* with 0.5 mM EDTA in HEPES buffer (pH 7.2) for four minutes. Cultures of rat liver hepatocytes were incubated with the test material for 18-20 hours. UDS was measures by electronically counting nuclear grains and subtracting the average number of grains in 3 adjacent nuclear-sized cytoplasmic areas. 75-150 cells were analyzed for each dose level. The test was considered positive if an increase in net nuclear grain counts of at least six grains per nucleus above the solvent control and/or an increase in the percent of nuclei with at least 6 net grains to more than 10% above the negative control value.
Results	Negative at all dose levels
Cytotoxic concentration	Non-toxic at all dose levels
Genotoxic Effects	None
Appropriate statistical evaluations?	Not given
Remarks for results	The test article did not cause a significant increase in UDS as measured by the mean number of net nuclear grain counts by any dose level. The positive control, 7,12-dimethylbenz(a)-anthracene (DMBA), induced significant increases in the mean number of net nuclear grain counts compared to the solvent control.
Conclusion Remarks	There was no increase in unscheduled DNA synthesis.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Heck J. D., Vollmuth, T. A., Cifone, M. A., Jagannath, D. R., Myhr B., and R.D. Curren (1989) An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist, 9(1), 257.

4.2.2 *In vivo* Genotoxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data for phenacetaldehyde, 2-methyl
Method/guideline	Sex linked recessive lethal mutation assay (Wuergler *et al*., 1977)
Test Type	Lethal mutation test
GLP	Ambiguous
Year	1983

Species/Strain	*Drosophila melanogaster*
Sex	Not reported
Route of Administration	Oral-Diet
Doses/Concentration	10 mM
Exposure Period	Not reported
Remarks for Test Conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Further details of the methodology were not reported.
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Number of sex-linked lethal/chromosomes tested in Brood 1, 3/1187. Brood II, 2/650, and Brood III, 2/1180.
Genotoxic effects	None
Remarks for Results	Ten mM solutions of phenylacetaldehyde, 2-methyl did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion Remarks	10 mM solutions of phenylacetaldehyde, 2-methyl did not induce sex linked recessive lethals in *Drosophila melanogaster*.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data for phenyacetic acid ester, isoeugenol phenylacetate
Method/guideline	Sex linked recessive lethal mutation assay (Wuergler *et al*., 1977)
Test Type	Lethal mutation test
GLP	Ambiguous
Year	1983
Species/Strain	*Drosophila melanogaster*
Sex	Not reported

Route of Administration	Oral-Diet
Doses/Concentration	25 mM
Exposure Period	Not reported
Remarks for Test Conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Further details of the methodology were not reported.
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Number of sex-linked lethal/chromosomes tested in Brood 1, 6/1223. Brood II, 2/1097, and Brood III, 1/1200.
Genotoxic effects	None
Remarks for Results	Twenty-five mM solutions of phenylacetic acid, isoeugenol ester did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion Remarks	Phenylacetic acid, isoeugenol ester did not induce sex linked recessive lethals in Drosophila melanogaster.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data for phenacetaldehyde, 2-methyl
Method/guideline	Micronucleus test
Test Type	Clastogenic assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	134, 402, or 670 mg/kg bw in olive oil

Exposure Period	One dose at 0 hours
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 hours with 134, 402, or 670 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976).
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 134, 402, and 670 mg/kg bw was 1.5, 2.3, 1.3, and 2.5, respectively
Genotoxic effects	None
Conclusion Remarks	Phenylacetaldehyde, 2-methyl did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data for phenylacetic acid ester, isoeugenol phenylacetate
Method/guideline	Micronucleus test
Test Type	Clastogenic assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	564, 987, or 1,410 mg/kg bw in olive oil
Exposure Period	Two doses at 0 and 24 hours
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 564, 987, or 1,410 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976).

Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 335, 670, and 1,005 mg/kg bw was 2.3, 1.3, 2.5, and 3.0, respectively.
Genotoxic effects	None
Conclusion Remarks	Phenylacetic acid, isoeugenol ester, did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

4.3 Repeated Dose Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Oral subchronic study
GLP	No
Year	1981
Species/strain	Rat
Sex	Male
Route of Administration	Oral-Gavage
Doses/concentration Levels	51 mg/kg bw/day
Exposure Period	4 months
Frequency of Treatment	Daily
Remarks for test conditions	Only liver function tests were conducted.
Control Group	Untreated
Post Exposure	None
Toxic Response/effects by Dose Level	Evidence of enzyme induction seen
Data Qualities Reliabilities	Reliability code 3. Not reliable.

Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods.
References	Zaitsev A. N. and Rakhmanina N. L. (1974) Some data on the toxic properties of phenylethyl and cinnamyl alcohols. Voprosy pitaniia, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data given for homologue phenethyl phenylacetate
Method/guideline	Oral subchronic study
GLP	No
Year	1967
Species/strain	Rat/Osborne Mendel
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	0, 1,000, 2,500 or 10,000 ppm approximately an average daily intake of 0, 50, 125, or 500 mg/kg bw.
Exposure Period	17 weeks
Frequency of Treatment	Daily
Control Group	Untreated diet
Post Exposure	None
Remarks for Test Conditions	Groups of ten male and ten female Osborne-Mendel rats were provided phenethyl phenylacetate in the diet at concentrations of 0, 1,000, 2,500 or 10,000 ppm which corresponds to an average daily intake of 0, 50, 125, or 500 mg/kg bw per day for 17 weeks. Measurements of body weight and food intake were recorded weekly.
NOAEL (NOEL)	10,000 ppm or 500 mg/kg bw
LOAEL (LOEL)	None
Actual dose received by dose level and sex	Not reported
Toxic Response/effects by Dose Level	No effects at any dose
Statistical Evaluation	Not given
Remarks for results	Measurement of body weight and food intake recorded weekly showed no significant difference between test and control animals at any intake level. At termination, hematological examinations revealed no effects due to administration of the test substance. At necropsy, no differences were reported in

	major organ weights between test and control animals. Gross examination of tissue of all animals was unremarkable and histopathological examination of six-eight animals, equally represented by gender, for the high-dose group and the control group revealed no treatment-related lesions.
Conclusion remarks	The NOAEL was determined to be greater than 500 mg/kg bw/d.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hagan E. C., Hansen W. H., Fitzhugh O. G., Jenner P. M., Jones W. I., Taylor J. M., Long E. L., Nelson A. A. and Brouwer J. B. (1967) Food Flavourings and Compounds of related Structure. II. Subacute and Chronic Toxicity. Food and Cosmetic Toxicology, 5, 141-157.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Test substance was administered as a mixture and included 6,000 mg/kg bw ethyl alcohol (6%), 4 mg/kg bw ethyl acetate (0.004%), 120 mg/kg bw isoamyl alcohol (0.12%), 120 mg/kg bw phenethyl alcohol (0.12%), 200 mg/kg bw isobutyl alcohol (0.2%), and 200 mg/kg bw acetic acid (0.2%).
Method/Guideline	Oral subchronic study
GLP	No
Year	1969
Species/strain	Rats/Wistar
Sex	Male and Female
Route of Administration	Oral-drinking water
Doses/concentration Levels	6,000 mg/kg bw ethyl alcohol (6%), 4 mg/kg bw ethyl acetate (0.004%), 120 mg/kg bw isoamyl alcohol (0.12%), 120 mg/kg bw phenethyl alcohol (0.12%), 200 mg/kg bw isobutyl alcohol (0.2%), and 200 mg/kg bw acetic acid (0.2%)
Exposure Period	56 weeks
Frequency of Treatment	Daily
Control Group	Yes, tap water only
Post Exposure	None
Remarks for Test Conditions	Groups of male and female Wistar albino rats (20/sex/group) were given a mixture of compounds dissolved in tap water as their only drinking source for 56 weeks. This mixture included 6,000 mg/kg bw ethyl alcohol (6%), 4 mg/kg bw ethyl acetate (0.004%), 120 mg/kg bw isoamyl alcohol (0.12%), 120 mg/kg

	bw phenethyl alcohol (0.12%), 200 mg/kg bw isobutyl alcohol (0.2%), and 200 mg/kg bw acetic acid (0.2%). A control group of 20 rats/sex was maintained on tap water only. Body weights were recorded weekly. The activity of alcohol dehydrogenase (ADH), glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and the protein content were determined at two-four week intervals in the livers of rats. At study termination, liver, kidney, heart, spleen, and lung were examined histologically.
Toxic Response/effects by Dose Level	There was a slight non-statistically significant decrease in the mean body weight of the test groups at 28-29 weeks compared to 53-56 weeks. There was no difference in absolute or relative liver weight between the test and control groups. There was a slight increase in GOT activity between 28 and 56 weeks in the test and control groups. No significant abnormalities were observed in any of the organs examined. Six animals contracted pneumonia and were discarded. Pneumonia was common in the rats at termination, equally distributed in all groups. The authors concluded that the mixture of chemicals tested did not produce any effects in the parameters tested.
Statistical Evaluation	Yes, Kruskal-Wallis test
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods.
References	Johannsen E. and Purchase I.F.H. (1969) Kaffircorn malting and brewing studies. XXI: The effect of the fusel oils of Bantu beer on rat liver. S.A. Medical Journal (Supplement- S.A. Journal of Nutrition, 43(12), 326-328.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity 99.8%
Method/Guideline	Subchronic study
GLP	Ambiguous
Year	1981
Species/strain	Rat/Charles River CD
Sex	Male and Female
Route of Administration	Dermal
Doses/concentration Levels	0.25, 0.5, 1.0 & 2.0 ml/kg bw/day
Exposure Period	90 days
Frequency of Treatment	Daily

Control Group	Untreated
Post Exposure	None
Remarks for Test Conditions	Groups of Charles River CD albino rats were administered 0.25, 0.5, 1.0 and 2.0 ml/kg bw/d for 90 days. Material applied to the shaved dorsal. Animals were observed daily for appearance and behavior changes. Parameters evaluated weekly-included weight gain, food intake. Funduscopic and biomicroscopic examinations were performed on the eyes of all animals. Biochemical analyses were also performed. Necropsies were performed on all animals.
NOAEL(NOEL)	0.5 ml/kg bw/day
LOAEL (LOEL)	1.0 ml/kg bw/day
Toxic Response/effects by Dose Level	Significant decreases in body weight gain and body weights were reported for both sexes at the two highest dose levels. Decreased hemoglobin and white blood cell counts were reported for the high dose males only. No findings were reported upon histopathological examination.
Statistical Evaluation	Yes
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards. Published in a peer-reviewed journal.
References	Owston E., Lough R. and Opdyke D.L. (1981) A 90-day study of phenylethyl alcohol in the rat. Fd and Cosmet Toxicol, 19(6), 713-715.

4.4 Reproductive Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data for principal animal metabolite, phenyl acetic acid
Method/Guideline	A 39-day reproduction/developmental-screening assay in SD rats. GLP Regs. FDA (1987)
Test Type	Reproductive/Developmental Toxicity Study
GLP	Yes
Year	1990
Species/Strain	Rat/Sprague-Dawley
Sex	Female/10/group
Route of Administration	Oral/gavage

Duration of Test	39 days
Doses/Concentration	250, 500 & 1000 mg/kg/day
Premating Exposure period for males	Not reported
Premating Exposure period for females	7 days
Control Group and Treatment	Corn oil vehicle, 5 ml/kg/day
Frequency of Treatment	Daily
Remarks for Test Conditions	Virgin female Sprague-Dawley rats (10/group) were orally administered a vehicle or the test material at 3 dosages for one week prior to a 7-day cohabitation period through gestation, parturition and a 4-day postpartum period. Study duration was 39 days. Maternal toxicity: Dams observed daily for clinical signs and were monitored for mortality, body weight, body weight gain, and food consumption. On day 25 of gestation dams were necropsied and examined for gross lesions. Reproductive performance was monitored in terms of mating index, fertility index, implantation sites per litter, duration of gestation, gestation index and litter size.
NOAEL(NOEL)	250 mg/kg/d (maternal NOAEL)
LOAEL(LOEL)	500 mg/kg/d (maternal LOAEL))
Appropriate statistical evaluations	ANOVA followed by Dunnett's test
Remarks for Results	The decreased body weights and food consumption reported at 250 mg/kg bw/d during premating period were not considered adverse. Based on the significant decrease in (P less than 0.05) in pup weight at birth and pup viability in the high-dose group, the NOAEL for the F1 offspring was reported to be 500 mg/kg bw/day.
Parental data and F1 as Appropriate	Maternal changes at 250 mg/kg bw included a statistically significant decrease in body weight and body weight gain that was accompanied by a decrease in food consumption. At the 50 and 1000 mg/kg bw levels, a significant (P less than 0.05) increase in mortality, clinical symptoms of toxicity, and decreased body weight gain and food consumption were reported. At necropsy gross lesion of the liver and other organs was reported. Mating index was decreased in the 1000 mg/kg bw dose group only. In dams included decreased activity and excess salivation during the pre-gestation period and increased (P less than 0.01) salivation in the high dose group during gestation. Significant (P less than 0.05 to less than 0.01) decreases in body weight and absolute and relative food consumption were measured during the premating period.
Offspring toxicity F1 and F2	Significant (P less than 0.05) decrease in pup viability and body weight occurred in the high dose groups compared to controls. No gross lesions in pups were attributable to administration of

	the test material.
Conclusion remarks	The NOAEL for maternal toxicity was 250 mg/kg bw/day and the NOAEL for reproductive performance was 250 mg/kg bw/day.
Remarks for Results	
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Vollmuth T.A., Bennett, M.B., Hoberman, A.M. and Christian, M.S. (1995) An Evaluation of Food Flavoring Ingredients Using an In Vivo Reproductive and Developmental Toxicity Screening Test. Teratology, 41(5), 597.

4.5 Developmental/Teratogenicity Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Not characterized
Test Type	Fetal developmental study
GLP	No
Year	1983
Species/strain	Rat/Long-Evans
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	20 days
Doses/concentration Levels	0, 4.3, 43 & 430 mg/kg bw/d
Exposure Period	Days 6 - 15 of gestation
Frequency of Treatment	Daily
Control Group and Treatment	Vehicle (water) only
Remarks for Test Conditions	The test material was dosed as an aqueous suspension. 19 rats in control group, 7 in low and mid-dose groups and 5 in high dose.
NOAEL(NOEL) maternal toxicity	43 mg/kg
LOAEL(LOEL) maternal toxicity	430 mg/kg

toxicity	
LOAEL (LOEL) developmental toxicity	4300 mg/kg
Actual dose received by dose level and sex	Not given
Maternal data with dose level	"Severe intoxication" at high dose and asymtomatic at 2 lower doses.
Fetal Data with Dose Level	The average birth weight and pup size of all treated groups were significantly lower than those of the control group, but the change was not dose-related. In fact, birth weights were greater in the mid-dose group than in controls. Mean litter size was greater in the high dose group (13) than in either the two lower doses (9) or controls (12). Also, embryolethality did not occur in the high dose group but was 18% at 43 mg/kg and 10% at 4.3 mg/kg. The authors reported a clear dose related increase in the percentage of malformations in live offspring (100% at the 432 mg/kg level, 93% at 43 mg/kg and 50% at 4.3 mg/kg). Malformations were mainly in ocular malformation, neural tube defects, hydronephrosis and limb defects.
Appropriate statistical evaluations	Yes
Remarks for Results	Dose response evident only on grouping of certain malformations. Often no dose response on individual effects or by grouping related effects.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Mankes R. F., LeFevre R., Bates H. and Abraham R. (1983) Effects of Various Exposure Levels of 2-Phenylethanol on Fetal Development and Survival in Long-Evans Rats. Journal of Toxicology and Environmental Health, 12, 235-244.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity 98.5%
Method/Guideline	Modified OECD 414
Test Type	Prenatal developmental
GLP	Yes
Year	1986
Species/strain	CrL:COBS CD (SD) BR
Sex	Female
Route of Administration	Dermal

Duration of Test	21 days
Doses/concentration Levels	140, 430 & 1400 mg/kg
Exposure Period	Days 6-15 of pregnancy
Frequency of Treatment	Daily
Control Group and Treatment	Water
Remarks for Test Conditions	Test was conducted according to OECD 414 except dosing was only during the period of organogenesis. The effect of phenethyl alcohol on pregnancy of rats was studied (Palmer *et al*., 1986). Phenethyl alcohol was applied topically at the dose of 0, 0.14, 0.43 or 1.40 ml/kg (approximately 143, 438, or 1430 mg/kg bw) during day 6 to 15 of pregnancy. The doses are approximately equal to 0, 140, 430, and 1400 mg/kg bw, respectively, and were chosen so that the intermediate dose was roughly equivalent to the highest dosage used in a previous oral study (Mankes *et al*., 1983). The highest dose was designed to extend the range in case of differential absorption by the dermal route. The animals were killed on day 20 of pregnancy and in utero development assessed by determination of litter values and examination of the fetuses for soft tissue and skeletal changes.
NOAEL(NOEL) maternal toxicity	430 mg/kg
LOAEL(LOEL) maternal toxicity	1400 mg/kg
NOAEL (NOEL) developmental toxicity	140 mg/kg
Actual dose received by dose level and sex	430 mg/kg
Maternal data with dose level	1400 mg/kg death of 3/35 and suppression of food intake and growth rate with clinical signs of toxicity. No significant effects at lower doses
Fetal Data with Dose Level	1400 mg/kg resorption of 5/23 litters, reductions in litter size and weight. Morphological change in 160/161 foetuses. 430 mg/kg increased incidence of foetuses with cervical rib bud and defects of thoracic vertebrae 140 mg/kg, no significant effects.
Appropriate statistical evaluations	Yes
Remarks for Results	Although fetal effects at 430 mg/kg were not considered serious according to the authors, this dose cannot be called a NOAEL.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Palmer A.K., Bottomley, A. M., Ratcliffe, H.E. Clark, R., and John, D. M. (1986) Effect of Phenylethyl Alcohol (PEA) on

Pregnancy of the Rat. Huntingdon Research Center. Unpublished report to RIFM.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity 99.6%
Test Type	Prenatal developmental dosage-range toxicity study
GLP	Yes
Year	1986
Species/strain	CrL:COBS CD (SD) BR
Sex	Female
Route of Administration	Dermal
Duration of Test	21 days
Doses/concentration Levels	70, 140, 280, 430 & 700 mg/kg
Exposure Period	Days 6-15 of pregnancy
Frequency of Treatment	Daily
Control Group and Treatment	Water
Remarks for Test Conditions	The test was conducted as a follow-up to Palmer, *et al.*, 1986 to better define the fetal and maternal NOAELs.
NOAEL(NOEL) maternal toxicity	Less than 70 mg/kg
LOAEL(LOEL) maternal toxicity	70 mg/kg
NOAEL (NOEL) developmental toxicity	140 mg/kg
Actual dose received by dose level and sex	280 mg/kg
Maternal data with dose level	Signs of dermal irritation were seen in all dosed groups.
Fetal Data with Dose Level	The NOEL for the cervical rib formation seen in Palmer *et al.* 1986 was 430 mg/kg. Other effects including incomplete ossification and decreased fetal body weight possibly as an indirect result of the maternal irritation were seen in all dose groups but were considered reversible effects. The only statistically significant difference from controls in the two lower dose groups was incomplete ossification of the pelvis but with no dose correlation.
Appropriate statistical evaluations	Yes

Conclusion Remarks	The study was compromised due to the dermal irritation seen at all dose levels.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Christian M.S. and Hoberman A.M. (1988) Dosage-range developmental toxicity (embryo/fetal toxicity and teratogenicity) study of 2-phenylethylalcohol (PEA) administered dermally to presumed pregnant mice. Unpublished report to RIFM

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data for principal animal metabolite, phenylacetic acid
Method/Guideline	A 39 day reproduction/developmental screening assay in SD rats. GLP Regs. FDA (1987)
Test Type	Virgin female Sprague-Dawley rats (10/group) were orally administered a vehicle or the test material at 3 dosages for one week prior to a 7-day cohabitation period through gestation, parturition and a 4-day postpartum period. Study duration was 39 days.
GLP	Yes
Year	1990
Species/strain	Rat/Sprague-Dawley
Sex	Female/10/group
Route of Administration	Oral-Gavage
Duration of Test	39 days
Doses/concentration Levels	250, 500 & 1000 mg/kg/day
Exposure Period	7 days premating, through gestation and 4 days postpartum (39 days)
Frequency of Treatment	Daily
Control Group and Treatment	Corn oil vehicle, 5 ml/kg/day
Remarks for Test Conditions	Virgin female Sprague-Dawley rats (10/group) were orally administered a vehicle or the test material at 3 dosages for one week prior to a 7-day cohabitation period through gestation, parturition and a 4-day postpartum period. Study duration was 39 days. Developmental toxicity was monitored in terms of mortality, viability (pups dying on days 1-4), pup body weight and pup body weight gain.
NOAEL(NOEL) maternal toxicity	250 mg/kg bw

LOAEL(LOEL) maternal toxicity	500 mg/kg bw
NOAEL (NOEL) developmental toxicity	500 mg/kg bw
LOAEL(LOEL) developmental toxicity	1000 mg/kg bw
Maternal data with dose level	Maternal changes at 250 mg/kg bw included a statistically significant decrease in body weight and body weight gain that was accompanied by a decrease in food consumption. At the 500 and 1000 mg/kg bw levels, a significant (P less than 0.05) increase in mortality, clinical symptoms of toxicity, and decreased body weight gain and food consumption (P less than 0.05) were reported. At necropsy gross lesions of the liver and other organs were reported. Mating index was decreased in the 1000 mg/kg bw dose group only. Effects in dams included decreased activity and excess salivation during the pre-gestation period and increased (P less than 0.01) salivation in the high dose group during gestation. Significant (P less than 0.05 to less than 0.01) decreases in body weight and absolute and relative food consumption were measured during the premating period.
Fetal Data with Dose Level	No effects on development were observed at 250 or 500 mg/kg bw. Offspring effects observed only at the highest dose included a statistically significant (P less than 0.05) decrease in viability and a non-significant decrease in body weight gain.
Appropriate statistical evaluations	ANOVA followed by Dunnett's test
Remarks for Results	The decreased body weights and food consumption reported at 250 mg/kg bw/d during premating period were not considered adverse. Based on the significant decrease in (P less than 0.05) in pup viability in the high-dose group, the NOAEL for the F1 offspring was reported to be 500 mg/kg bw/day.
Conclusion Remarks	The NOAEL for development of offspring is 500 mg/kg bw/day.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Vollmuth T.A., Bennett, M.B., Hoberman, A.M. and Christian, M.S. (1995) An Evaluation of Food Flavoring Ingredients Using an In Vivo Reproductive and Developmental Toxicity Screening Test. Teratology 41(5), 597.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Blended commercial sample, purity 98.5%, from 4 manufacturers spray dried with gum Arabic at a concentration of 17.6%.
Method/Guideline	Essentially the same as OECD 414 except dosing was on days 6 – 16 of pregnancy.

	6 – 16 of pregnancy.
Test Type	Prenatal Developmental Toxicity Study
GLP	Yes
Year	1987
Species/strain	CrL: COBS CD(SD)BR rats
Sex	Female
Route of Administration	Oral-Diet
Duration of Test	20 days
Doses/concentration Levels	0, 1000, 3000 & 5000 ppm resulting in intakes of about 83, 266 & 799 mg/kg/day.
Exposure Period	Days 6-15 of pregnancy
Frequency of Treatment	Daily
Control Group and Treatment	Gum Arabic
Remarks for Test Conditions	Microencapsulation in Gum Arabic was used to prevent decreased food intake due to inappetence. Bioavailability was demonstrated in separate study (Hawkins *et al*., 1990).
NOAEL(NOEL) maternal toxicity	5000 ppm
LOAEL(LOEL) maternal toxicity	None
NOAEL (NOEL) developmental toxicity	5000 ppm
LOAEL(LOEL) developmental toxicity	None
Actual dose received by dose level and sex	Mean daily intakes during days of dosing were 83.1, 265.9 & 799.1 mg/kg.
Maternal data with dose level	No effects at any dose.
Fetal Data with Dose Level	No effects at any dose.
Appropriate statistical evaluations	Yes
Remarks for Results	The study was conducted to determine the effect of route of dosing on developmental toxicity.
Conclusion Remarks	There was no evidence of maternal or fetal toxicity at any dose level after dietary administration.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Bottomley A. M., Ratcliffe H. E., John D. M., Anderson A., Dawe I. S. (1987) Effect of Dietary Administration of Micro-

Encapsulated Phenylethyl Alcohol on Pregnancy of the Rat (Embryotoxicity Study). Unpublished Report to RIFM.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Embryotoxicity
GLP	No
Year	1973
Species/strain	Rats/Mongrel white
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	20 days
Doses/concentration Levels	508 mg/kg
Exposure Period	Once on 4th day of pregnancy or once during 10-12th day.
Frequency of Treatment	Once
Control Group and Treatment	Solvent only
Remarks for Test Conditions	Administered in sunflower oil.
Actual Dose Received by Dose Level and Sex	508 mg/kg
Maternal data with Dose Level	No maternal data reported
Fetal Data with Dose Level	Single dose level of 508 mg/kg caused no effects when administered at the 4th day of pregnancy but caused slight retardation of ossification when administered during the 10-12th day.
Appropriate Statistical Evaluations	Not reported
Remarks for Results	While study is poorly reported, results are consistent with other studies.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Method not validated.
References	Maganova N.B. and Zaitsev A.N. (1973) Study of the Embryotoxic Action of Some Synthetic Food Flavourings. Vopr Pitan, 32(4), 50-54.